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Review

Phytochemistry and pharmacologic properties of *Myristica fragrans* Hoyutt.: A review

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***Myristica fragrans* is known as "nutmeg", its extracts and essential oil are important in drug development with numerous pharmacological activities in South Africa, India and other tropical countries. For a long time, *M. fragrans* has been used in traditional medicines as a carminative, stimulant, narcotic, emmenagogue and abortifacient. Nutmeg is also prescribed for the treatment of many diseases, such as rheumatism, muscle spasm, decreased appetite and diarrhea. *M. fragrans* has recently been shown to have antioxidant, anticonvulsant, analgesic, anti-inflammatory, antidiabetic, antibacterial and antifungal activities. Trimyristin, myristic acid, myristicin, safrole and elimicin are reported from nutmeg. Due to the easy collection of nutmeg and being widespread and also remarkable biological activities, it has become both food and medicine in tropical countries especially in India and China. This article presents comprehensive analyzed information on the botanical, chemical and pharmacological aspects of *M. fragrans*.**

Key words: *Myristica fragrans*, Myristicaceae, phytopharmacology, essential oil.

INTRODUCTION

Myristica fragrans is commonly known as "nutmeg", it produces two spices: mace and nutmeg. Nutmeg is the seed kernel inside the fruit and mace is the red lacy covering (aril) on the kernel. *M. fragrans* belongs to Myristicaceae family in the order Magnoliales which contains about 150 genera and more than 3000 species. *Myristica* species are natives of Moluccas, indigenous to India, Indonesia and Sri Lanka and now cultivated in many tropical countries of both hemispheres as well as in South Africa (Pal et al., 2011). *Myristica* genus has nine species. *M. fragrans* has been known as "Joz-e-Buya" in Iran.

M. fragrans is a spreading aromatic evergreen tree usually growing to about 5 to13 m high, occasionally 20 m (Figure 1). The bark contains watery pink or red sap. The pointed dark green leaves (5 to 15 cm × 2 to 7 cm) are arranged alternately along the branches and are borne on leaf stems about 1 cm long. Upper leaf surfaces are shiny. Flowers are usually single sexed; occasionally male and female flowers are found on the same tree.

Female flowers arise in groups of 1 to 3; males in groups of 1 to 10. Flowers are pale yellow, waxy, fleshy and bell-shaped (Figure 2). Male flowers are 5 to 7 mm long; female flowers are up to 1 cm long. The fruits are fleshy, drooping, yellow, smooth, 6 to 9 cm long with a longitudinal ridge (Figure 3). When ripe, the succulent yellow fruit coat splits into two halves revealing a purplish-brown, shiny seed (nutmeg) surrounded by a red aril (mace) (Figure 4).

Seeds (nutmegs) are broadly ovoid (2 to 3 cm long), firm, fleshy, whitish and transversed by red-brown veins. When fresh, the aril (mace) is bright scarlet becoming more horny, brittle and with a yellowish-brown color when dried (Figure 5).

Nutmeg is popular as a spice and also possesses various therapeutic properties. Nutmeg has a characteristic pleasant fragrance and a slightly warm taste. It is used to flavor many kinds of baked foods, confections, puddings, meats, sausages, saucers, vegetables and beverages.

It is also used as components of curry powder, teas and soft drinks or mixed in milk and alcohol (Olaleye et al., 2006). For a long time, *M. fragrans* has been

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Figure 1. *M. fragrans* tree.

Figure 2. *M. fragrans* flowers.

Figure 4. *M. fragrans* kernel covered with red aril (mace).

Figure 3. *M. fragrans* fruits.

Figure 5. *M. fragrans* dried kernel (nutmeg).

used as a folklore medicine for treating diarrhea, mouth sores and insomnia (Somani and Singhai, 2008). Since the Middle Ages, nutmeg has been used as a stomachic, stimulant, carminative as well as for intestinal catarrh and colic, to stimulate appetite, to control flatulence and has a reputation as an emmenagogue and abortifacient (Min et al., 2011). The essential oil of nutmeg is used externally for rheumatism and possesses analgesic and anti-inflammatory properties (Santos et al., 1997; Olajide et al., 1999).

Compounds isolated from the seeds of this plant have been reported to possess strong platelet anti-aggregatory activity (Venton et al., 1991; Somani and Singhai, 2008). Also, nutmeg prevents hypercholesterolemia and atherosclerosis (Sharma et al., 1996). It has also been found to be useful as tonic for the heart and brain and also in sexual and general debility (Olaleye et al., 2006). The presence of two compounds, myristicin and elemicin, is often related to intoxication and hallucinogenic action of nutmeg, while safrole has been suspected to be carcinogenic. However, the mechanism by which these compounds act is still a subject of extensive research (Jukic et al., 2006).

Crude extract of nutmeg was reported to have chemopreventive and anti *Helicobacter pylori* activities (Bhamarapravati et al., 2006). It has shown tyrosine phosphatase 1B inhibitory, hepatoprotective and acetylcholine esterase inhibitory activities (Min et al., 2011). Medicinally, it is used as an anti-diarrheal agent for patients with medullar carcinoma of the thyroid. The effectiveness of the treatment may be due to the inhibition of prostaglandin synthesis in the mucosa and sub mucosa of the colon (Olaleye et al., 2006). *M. fragrans* extract effect on increasing the mounting behavior and mating performance of male Swiss mice has been reported (Tajuddin et al., 2003). For its role as an anti-cancer agent, myristicin, found in *M. fragrans* has cytotoxic and apoptotic effects in human neuroblastoma SK-N-SH cells with an accumulation of cytochrome and activation of caspase 3 in the cytosol (Lee et al., 2005).

Since review and systemic analysis of chemistry, pharmacology and clinical properties of *M. fragrans* have not been reported, the currently available information on traditional and local knowledge, ethno biological and ethno medicinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant was provided. The aim of the present review was to introduce *M. fragrans* as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

CHEMICAL COMPOSITION

The commonly known phytochemical compounds of *M. fragrans* are volatile substances, terpenoids, phenolics, lignin compounds, protein, mucilage and starch (Chirathaworn et al., 2007; Naikodi et al., 2011; El-Alfy et al., 2009). Alkaloids, saponins, anthraquinones, cardiac glycosides, flavonoids and phlobatanins were also detected in the aqueous extract of *M. fragrans* (Olaleye et al., 2006). Nutmeg volatile oil is comprised of a mixture of terpenes and alkenylbenzene derivatives. Myristicin, safrole and elimicin constitute about 80% of the alkenylbenzene derivatives (Janssen and Lackman, 1990; Evans, 1996).

Bioactive compounds including camphene, elemicin, eugenol, isoelemicin, isoeuglenol, methoxyeugenol and elimicin were identified as the main constituents of *M. fragrans* seed essential oil (Chirathaworn et al., 2007). Sabinene (41.7), α-pinene (9.4%), β-pinene (7.3%), terpine-4-ol (5.8%), limonene (3.7%), safrole (1.4%) and myristicin (2.7%) were also characterized in the essential oil of nutmeg collected from Andaman Nicobar Island (Pal et al., 2011). Sabinene (19.07%), α-pinene (18.04%), 4-terpineol (11.83%), limonene (8.32%) and β-pinene (7.92%) were identified as the major compounds of the essential oil of *M. fragrans* leaf (Zachariah et al., 2008).

Miristic acid, trimyristin (Figure 6), glycerides, stearic, lauric, linoleic and palmitic acids were the main components of nutmeg fixed oil (Duarte et al., 2011). Erythro-austrobailignan-6, meso-dihydroguaiaretic acid and nectandrin-B together with macelignan, machilin F, nectandrin B, licarin A, licarin B, myristagenol and meso-dihydroguaiaretic acid are lignans isolated from *M. fragrans* seeds (Cho et al., 2007; Lee et al., 2009). Some lignin compounds including (8R,8'S)-7'-(3',4'-methyl enedioxyphenyl)-8,8'-dimethyl - 7- (3, 4 - dihydroxy - phenyl)-butane, meso-monomethyl dihydroguaiaretic acid, (+)-guaiacin, (7S,8'R,7'R)-4,4'-dihydroxy-3,3'-di methoxy-7',9-epoxylignan, 7-(4-hydroxy-3-methoxy-phenyl)-7-(3,4-methylenedioxyphenyl)-8,8-lignan -7-methylether and (8R,8'S)-7-(3,4-methylene-dioxyphenyl)-8-methyl-8'-hydroxymethyl-7'-(3',4'-methylenedioxy-phenyl)-butanol were also isolated from *M. fragrans* seeds (Min et al., 2011).

Two new phenolic compounds, (−)-1-(2,6-dihydroxyphenyl)-9-[4-hydroxy-3-(p-menth-1-en-8-oxy)-phenyl]-1-nonanone and (7R,8R)-7,8-dihydro-7-(3,4-dihydroxyphenyl)-3′-methoxy-8-methyl-1′-(E-propenyl)-benzofuran were characterized for the first time in the fruits of *M. fragrans* (Duan et al., 2009).

Mace, the dried seed covers of *M. fragrans,* is also aromatic and its aroma is due the presence of terpenes. Depending on its origins, mace has 7 to 14% essential oil and about 30% fixed oil. It contains the same aroma compounds as nutmeg but in different amounts, mainly monoterpenes (87.5%), monoterpene alcohols (5.5%), and other aromatics (7%). Like nutmeg essential oil, the main constituents of mace essential oil are sabinene, α-pinene, myrcene, limonene, 1,8-cineole, terpinen-4-ol, myristicin, γ-terpinene and safrole (Pooja et al., 2012). Malabaricone B and malabaricone C are two resorcinols

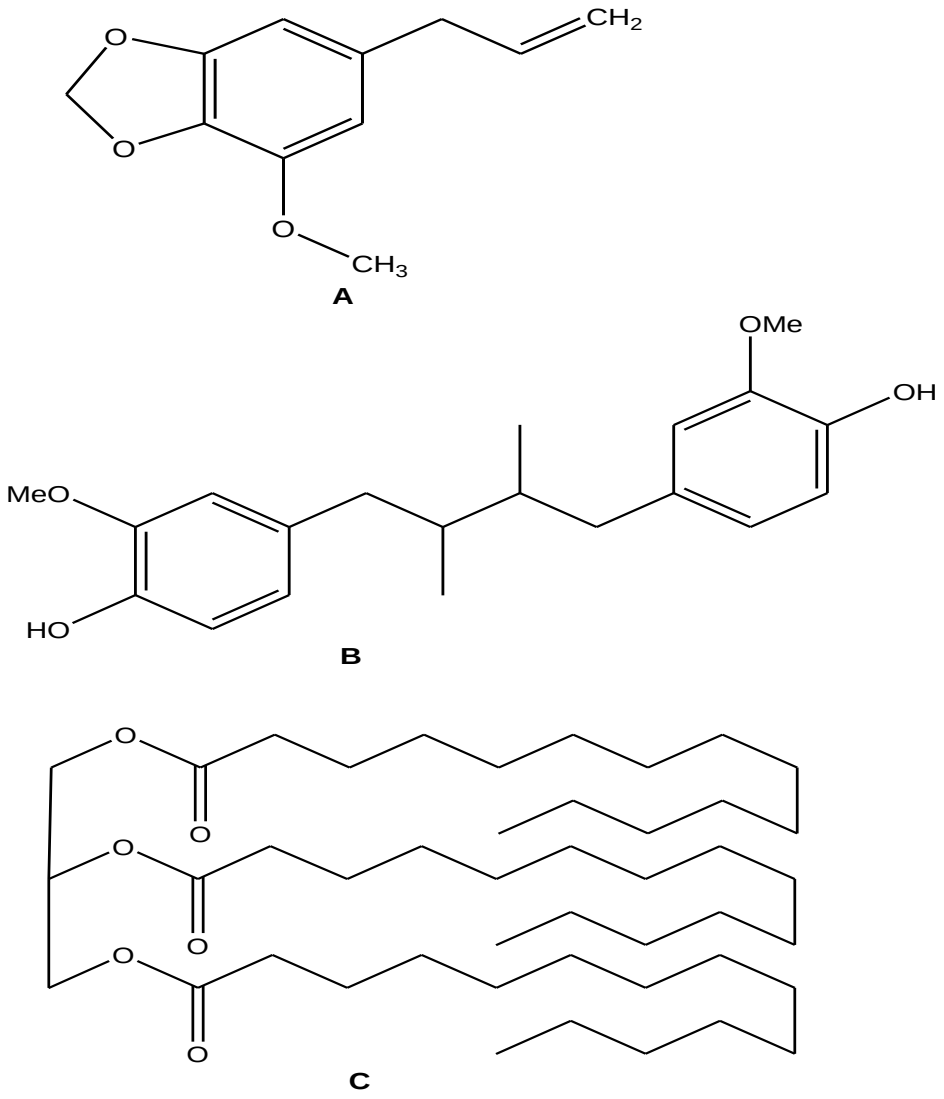

Figure 6. Structures of A, myristicin; B, dihydroguaiaretic acid; C, trimyristin from *M. fragrans*.

isolated from mace (Orabi et al., 1991).

ANTI-INFLAMMATORY AND ANALGESIC PROPERTIES

Although a number of steroidal or non-steroidal anti-inflammatory drugs have been developed, researchers are changing their focus on natural products to develop new anti-inflammatory agents due to the side-effects of chemical drugs (Hyun and Kim, 2009; Shokrzadeh and Saeedi, 2009). As a result, the search for other alternatives seems necessary and beneficial. Many cells and mediators are involved in proceeding inflammation. For example, macrophages are representative inflammatory cells involved in acute or chronic inflammatory responses by over-production of pro-inflammatory cytokines [for example, tumor necrosis factor (TNF)-a, interleukin (IL)-1b and granulocyte/macrophage colony stimulating factor (GMCSF)] and inflammatory mediators (Rhee et al., 2009; Lundberg, 2003; Walsh, 2003). Essential oil of nutmeg and mace are traditionally used to relief sprains, rheumatism and paralysis (Chatterjee and Pakrashi, 1992). The petroleum ether extract showed activities similar to non-steroidal anti-inflammatory drugs (Olajide et al., 2000).

The chloroform extract also inhibited the carrageenan induced edema in rats (Olajide et al., 1999). The methanol extract showed a lasting anti-inflammatory activity. Results suggest that the anti-inflammatory action is due to the myristicin present in nutmeg. Myristicin is a phenylpropene, a natural organic compound present in small amounts in essential oil of nutmeg (Naikod et al.,

2011).

NEUROPHARMACOLOGIC PROPERTIES

Many central nervous system (CNS) activities have been reported for nutmeg. Trimyristin and the hexane extract of nutmeg demonstrated anxiogenic activity in mice (10 to 100 and 30 to 300 mg/kg, intraperitoneally (i.p.), respectively) when tested in the elevated plus maze and the hole-board paradigms (Sonavane et al., 2002b). The hexane extract of the seeds also exhibited antidepressant activity [10 mg/kg, orally (p.o.)] in mice using the forced swim and tail suspension tests (Sonavane et al., 2002a). Interaction of the extract with adrenergic, dopaminergic and serotonergic receptors has been proposed to mediate the antidepressant (Dhingra and Sharma, 2006). Oral administration of the hexane seed extract at 5 mg/kg dose for three successive days improved learning and memory in both young and aged mice as well as reversed the diazepam and scopolamine-induced learning and memory impairment (Parle et al., 2004). Inhibition of acetylcholinesterase activity has been suggested as potential mechanism for memory enhancement based on both *in vitro* and *in vivo* studies (Dhingra et al., 2006).

Earlier reports listed nutmeg as a recreational drug commonly used by teenagers as a cheap marijuana substitute. In fact the pain relieving capacity of nutmeg has been historically utilized to ward off pain, and as such has been commonly used to substitute morphine narcotic drugs (Rudgley, 1998). As mentioned earlier, the reputed psychoactivity of nutmeg has always been associated with the hypothesis of potential metabolic activation of nutmeg constituents to amphetamine-like compounds. Hence, this study compared the neuro-pharmacological actions of different nutmeg extracts with the actions of these commonly abused drugs, Δ-tetrahydrocannabinol, morphine and amphetamine (El-Alfy et al., 2009).

ANTICONVULSANT ACTIVITY

M. fragrans hexane extract possesses anticonvulsant activity against the animal models of Grand mal, Petit mal and status epilepticus. Decreased dopaminergic transmission may be partly responsible for its anti-convulsant effect (Sonavan et al., 2002).

Nutmeg essential oil was also found to possess significant anticonvulsant activity against electroshock-induced hind limb tonic extension. It exhibited dose dependent anticonvulsant activity against pentylenete trazole induced tonic seizures. It delayed the onset of hind limb tonic extensor jerks induced by strychnine. Also, it was anticonvulsant at lower doses, whereas weak proconvulsant at a higher dose against pentylenete trazole and bicuculline induced clonic seizures (Wahab et al., 2009).

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

The extract of *M. fragrans* showed antibacterial activity against *Staphylococcus aureus, Proteus vulgaris* and *Klebsiella pneumonia.* The extract was not effective against *Pseudomonas aeruginosa, Salmonella typhimurium* and *Bacillus subtilis* (Ibrahim et al., 2011).

Use of essential oils from edible plants is an attractive alternative method to control food/feed fungi as they should, in principle, not be toxic to man and could replace toxic synthetic fungicides. Use of nontoxic natural compounds is attributed to growing problems encountered with microbial resistance towards conventional preservation with synthetic fungicides and an increasing demand for minimal processed food along with “green” image policies of food industry. Nutmeg essential oil at a concentration of 0.1% inhibited radial growth of *Colletotrichum gloeosporoides* (98%), *Colletotrichum musae* (97%), *Fusarium oxysporum* (75%), *Fusarium semitectum* (78%), *Aspergillus niger* (71%) and *Aspergillus glaucus* (60%). Growth inhibition increased from 85 to 100% at a concentration of 0.3% (Valente et al., 2011).

Three antifungal lignans including erythro-austrobailignan-6 (EA6), meso-dihydroguaiaretic acid (MDA) and nectandrin-B (NB) were isolated from the methanol extract of *M. fragrans* seeds and showed activities against fungal strains such as *Alternaria alternata, Colletotrichum coccodes*, *Colletotrichum gloeosporioides, Magnaporthe grisea, Agrobacterium tumefaciens, Acidovorax konjaci* and *Burkholderia glumae* (Cho et al., 2007).

Reports have revealed the methanol extract of *M. fragrans* arils (mace) to have good activity against both the fungal strains, *Candida albicans* (0.237 mg/ml) and *A. niger* (0.232 mg/ml) (Pooja et al., 2012).

Dihydroguaiaretic acid (Figure 6) from mace has also shown activities against *H. pylori* with MIC of 100 µg/ml and MBC of 125 µg/ml. This effect is comparable with that of clarithromycin (MIC 120 µg/mL) (Bhamarapravati et al., 2006). The two antimicrobial resorcinols, malabaricone B and malabaricone C from *M. fragrans* mace also exhibited strong antifungal and antibacterial activities (Orabi et al., 1991).

ANTIDIABETIC PROPERTIES

Petroleum ether extract of *M. fragrans* decreased blood glucose levels in normal, glucose fed and alloxan-induced diabetic rats. The hypoglycaemic effect may be due to the potentiation of insulin release from beta-cells. Oral administration of the extract also suppressed the increase in glucose level induced by glucose loading.

This effect might be due to decrease in the rate of intestinal glucose absorption or potentiation of pancreatic secretions or increasing the glucose uptake. The extract increased body weight in diabetic animals, which might be due to increased insulin secretion and better glyceamic control (Somani and Singhai, 2008). Administration of ethanolic extract of *M. fragrans* fruits to streptozotocin (STZ)-induced diabetic rats also resulted in moderate lowering in blood glucose. Lowering in blood glucose was found to be from 3 to 7 h post treatment. Peak lowering in blood glucose was observed at 7 h post treatment (Ahmad et al., 2008). Thus, *M. fragrans* possesses potential as an antidiabetic and warrants the need for further studies to elucidate its mode of action.

CONCLUSION

The objective of this review was to show the recent advances in the exploration of *M. fragrans* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *M. fragrans* has pharmacological functions including anti-inflammatory, analgesic, anti-convulsant, antibacterial, antifungal and antioxidant activities, among others. As the current information shows, it is also possible that furanocoumarins might be useful in the development of new drugs for the treatment of various diseases. However, the present results suggest a possibility that furanocoumarins can be further developed as a potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *M. fragrans*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism will be a focus for future studies. Last but not the least, this review emphasizes the potential of *M. fragrans* to be employed in new therapeutic drugs and provide the basis for future research on the application of transitional medicinal plants.

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